FORM PTO-1390 (Modified) (REV 5-93) U.S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: 040283-0199

		U.S. APPLICATION NO. (If known, see 37 CFR 1.5): Unassigned 10/031708
INTERNATIONAL APPLICATION NO. PCT/GB00/02817	INTERNATIONAL FILING DATE 07/21/2000	PRIORITY DATE CLAIMED 07/23/1999

TITLE OF INVENTION
CHEMICAL COMPOUNDS-III

APPLICANT(S) FOR DO/EO/US
Mike Frederick SNAPE

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.

2. ☐ This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.

3. ☐ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).

4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   - ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   - ☒ has been transmitted by the International Bureau.
   - ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)

6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   - ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   - ☐ have been transmitted by the International Bureau.
   - ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   - ☒ have not been made and will not be made.

8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).

9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).

10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

11. ☒ Applicant claims small entity status under 37 CFR 1.27 .

Items 12. to 17. below concern other document(s) or information included:

12. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

13. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

14. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.

15. ☐ A substitute specification.

16. ☐ A change of power of attorney and/or address letter.

17. ☐ Other items or information:

531 Rec'd PC 23 JAN 2001

U.S. APPLICATION NO. (If known, see 37 C.F.R. 5~~10/031708~~	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
Unassigned	PCT/GB00/02817	040283-0199

18. ☒ The following fees are submitted:	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5): Search Report has been prepared by the EPO or JPO.....$890.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482).....$710.00		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2) $740.00		
Neither international preliminary examination fee (37 CFR 1.482) nor International search fee (37 CFR 1.445(a)(2)) paid to USPTO $1,040.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) $100.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$890.00	
Surcharge of $130.00 for furnishing the oath or declaration later than 20 Months from the earliest claimed priority date (37 CFR 1.492(e))	$130.00	

Claims	Number Filed		Included in Basic Fee		Extra Claims		Rate		
Total Claims	23	-	20	=	3	×	$18.00	$54.00	
Independent Claims	1	-	3	=	0	×	$84.00	$0.00	
Multiple dependent claim(s) (if applicable)							$280.00		
TOTAL OF ABOVE CALCULATIONS =								$1074.00	
Reduction by ½ for filing by small entity, if applicable.								$537.00	
SUBTOTAL =								$537.00	
Processing fee of $130.00 for furnishing English translation later the 20 months from the earliest claimed priority date (37 CFR 1.492(f). +									
TOTAL NATIONAL FEE =								$537.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property +									
TOTAL FEES ENCLOSED =								$537.00	

				Amount to be:	
				refunded	$
				charged	$

a. ☒ A check in the amount of $537.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 19-0741 in the amount of $537.00 to the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-0741. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Foley & Lardner
Customer Number: 22428

22428

PATENT TRADEMARK OFFICE

SIGNATURE

NAME BERNHARD D. SAXE

REGISTRATION NUMBER 28,665

Atty. Dkt. No. 040283-0199

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Mike Frederick SNAPE

Title: CHEMICAL COMPOUNDS-III

Appl. No.: Unassigned

Filing Date: January 23, 2002

Examiner: Unassigned

Art Unit: Unassigned

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

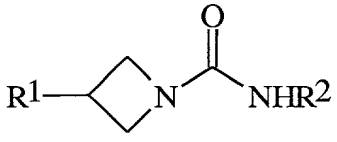
Sir:

Prior to examination of the above-identified application, Applicant respectfully requests that the following amendments be entered into the application:

IN THE CLAIMS:

In accordance with 37 C.F.R. § 1.21, please substitute for original claims 1-23 the following rewritten version of the same claims, as amended. The changes are shown explicitly in the attached "Version With Markings to Show Changes Made". Please also cancel claims 24-26 without prejudice or disclaimer.

1. (Amended) A method of neuroprotection or treatment of cerebral ischaemia, central nervous system injury or eye diseases, comprising administration to a subject in need of such treatment an effective amount of a compound of formula (I)



(I)

wherein

R^1 is aryl; and

R^2 is hydrogen or alkyl;

or a pharmaceutically acceptable salt or prodrug thereof.

2. (Amended) A method according to claim 1, wherein R^1 is an unsubstituted or substituted phenyl or naphthyl group.

3. (Amended) A method according to claim 1, wherein R^1 has 1, 2 or 3 substituent groups.

4. (Amended) A method according to claim 1, wherein R^1 is substituted with one or more substituent groups selected from the group consisting of halo, trifluoromethyl and tertiary-butyl.

5. (Amended) A method according to claim 4, wherein said halo groups are chloro or fluoro.

6. (Amended) A method according to claim 2, wherein R^1 is a meta- or para-substituted phenyl group.

7. (Amended) A method according to claim 2, wherein R^1 is selected from the group consisting of 4-chlorophenyl, 4-fluorophenyl, 4-(trifluoromethyl)phenyl and 3-(trifluoromethyl)phenyl.

8. (Amended) A method according to claim 2, wherein R^1 is selected from the group consisting of 2,3-disubstituted phenyl, 2,4-disubstituted phenyl, 3,4-disubstituted phenyl and 3,5-disubstituted phenyl.

9. (Amended) A method according to claim 4, wherein R^1 is substituted by two halo groups, the same or different, or by one halo group and one trifluoromethyl group.

10. (Amended) A method according to claim 9, wherein R^1 is dichloro-substituted, difluoro-substituted, chloro-fluoro-substituted or fluoro-trifluoromethyl-substituted.

11. (Amended) A method according to claim 10, wherein R^1 is selected from the group consisting of 3,4-dichlorophenyl, 3,4-difluorophenyl, 3-chloro-4-fluorophenyl, 4-chloro-3-fluorophenyl, 3-fluoro-4-(trifluoromethyl)phenyl, 4-fluoro-3-(trifluoromethyl)phenyl and 3-chloro-5-fluorophenyl.

12. (Amended) A method according to claim 1, wherein R^2 is alkyl.

13. (Amended) A method according to claim 12, wherein R^2 is C_{1-8} alkyl.

14. (Amended) A method according to claim 1, wherein R^2 is alkenyl, alkynyl, hydroxyalkyl or alkoxyalkyl.

15. (Amended) A method according to claim 1, wherein R^2 is unsubstituted saturated cyclic or acyclic hydrocarbyl.

16. (Amended) A method according to claim 1, wherein R^2 is propyl, 2-propenyl, 2-propynyl or 2-hydroxypropyl.

17. (Amended) A method according to claim 1, wherein the compound of formula (I) is selected from the group consisting of:

(R)-3-(4-Fluorophenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide;

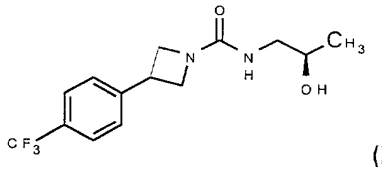
(3-(4-Chlorophenyl)-*N*-(2-propynyl)azetidine-1-carboxamide;

(*S*)-3-(4-Fluorophenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide; and

(S)-3-(4-(Trifluoromethyl)phenyl)-*N*-(2-hydroxypropyl)azetidine carboxamide.

18. (Amended) A method according to claim 1, wherein the compound of formula (I) is 3-(4-(trifluoromethyl)phenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide.

19. (Amended) A method according to claim 1, wherein the compound of formula (I) is the (*R*) enantiomer of 3-(4-(trifluoromethyl)phenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide (**Ib**), substantially free of its *(S)*-enantiomer.



(Ib)

20. (Amended) A method according to claim 1, wherein said compound is administered in combination with a pharmaceutically acceptable carrier.

21. (Amended) A method according to claim 20, wherein said carrier comprises a cyclodextrin or an ether derivative thereof.

22. (Amended) A method according to claim 20, wherein said carrier further comprises a buffer system, an isotonizing agent and water.

23. (Amended) A method according to claim 1, wherein said compound of formula (I) is administered in combination with one or more additional drugs useful in neuroprotection or in the treatment of cerebral ischaemia, central nervous system injury or eye diseases, the components being in the same formulation or in separate formulations for administration simultaneously or sequentially.

REMARKS

Applicants respectfully request that the foregoing amendments be made prior to examination of the present application.

Respectfully submitted,

Date: January 23, 2002

By _____

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Bernhard D. Saxe
Attorney for Applicant
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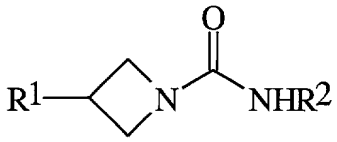
VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended) [Use] A method of neuroprotection or treatment of cerebral ischaemia, central nervous system injury or eye diseases, comprising administration to a subject in need of such treatment an effective amount of a compound of formula (I)



(I)

wherein

R^1 is aryl; and

R^2 is hydrogen or alkyl;

or a pharmaceutically acceptable salt or prodrug thereof [in the manufacture of a medicament for neuroprotection in a subject or for the treatment of cerebral ischaemia, central nervous system injury or eye diseases].

2. (Amended) A [use] method according to claim 1, wherein R^1 is an unsubstituted or substituted [aryl group selected from] phenyl or [and] naphthyl group.

3. (Amended) A [use] method according to claim 1, [or 2] wherein R^1 has 1, 2 or 3 substituent groups.

4. (Amended) A [use] method according to [any preceding] claim 1, wherein R^1 is substituted with one or more substituent groups selected from the group consisting of halo, trifluoromethyl and tertiary-butyl.

5. (Amended) A [use] method according to claim 4, wherein said halo groups are [selected from] chloro [and] or fluoro.

6. (Amended) A [use] method according to claim [1,] 2, [3, 4 or 5] wherein R^1 is a meta- or para-substituted phenyl group.

7. (Amended) A [use] method according to claim [1] 2, wherein R^1 is selected from the group consisting of 4-chlorophenyl, 4-fluorophenyl, 4-(trifluoromethyl)phenyl and 3-(trifluoromethyl)phenyl.

8. (Amended) A [use] method according to claim [1,] 2, [3, 4 or 5] wherein R^1 is selected from [a] the group consisting of 2,3-disubstituted phenyl [group], 2,4-disubstituted phenyl [group], 3,4-disubstituted phenyl [group] and [a] 3,5-disubstituted phenyl [group].

9. (Amended) A [use] method according to claim [8] 4, wherein R^1 is substituted by two halo groups, the same or different, or by one halo group and one trifluoromethyl group.

10. (Amended) A [use] method according to claim 9, wherein R^1 is dichloro-substituted, difluoro-substituted, chloro-fluoro-substituted or fluoro-trifluoromethyl-substituted.

11. (Amended) A [use] method according to claim [1] 10, wherein R^1 is selected from the group consisting of 3,4-dichlorophenyl, 3,4-difluorophenyl, 3-chloro-4-fluorophenyl, 4-chloro-3-fluorophenyl, 3-fluoro-4-(trifluoromethyl)phenyl, 4-fluoro-3-(trifluoromethyl)phenyl and 3-chloro-5-fluorophenyl.

12. (Amended) A [use] method according to [any one of claims] claim 1, [to 11] wherein R^2 is alkyl.

13. (Amended) A [use] method according to [any one of claims 1 to] claim 12, wherein R^2 is C_{1-8} alkyl.

14. (Amended) A [use] method according to [any one of claims] claim 1, [to 13] wherein R^2 is alkenyl, alkynyl, hydroxyalkyl or alkoxyalkyl.

15. (Amended) A [use] method according to [any one of claims] claim 1, [to 13] wherein R^2 is unsubstituted saturated cyclic or acyclic hydrocarbyl.

16. (Amended) A [use] method according to [any one of claims] claim 1, [to 13] wherein R^2 is propyl, 2-propenyl, 2-propynyl or 2-hydroxypropyl.

17. (Amended) A [use] method according to claim 1, wherein the compound of formula (I) is selected from the group consisting of:

(R)-3-(4-Fluorophenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide;

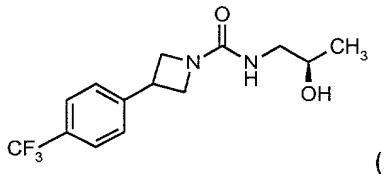
(3-(4-Chlorophenyl)-*N*-(2-propynyl)azetidine-1-carboxamide;

(*S*)-3-(4-Fluorophenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide; and

(S)-3-(4-(Trifluoromethyl)phenyl)-*N*-(2-hydroxypropyl)azetidine carboxamide [or a pharmaceutically acceptable salt or prodrug thereof].

18. (Amended) A [use] method according to claim 1, wherein the compound of formula (I) is 3-(4-(trifluoromethyl)phenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide [or a pharmaceutically acceptable salt or prodrug thereof].

19. (Amended) A [use] method according to claim 1, wherein the compound of formula (I) is the (*R*) enantiomer of 3-(4-(trifluoromethyl)phenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide **(Ib)** substantially free of its *(S)*-enantiomer.



(Ib)

[or a pharmaceutically acceptable salt or prodrug thereof, substantially free of its (*S*)-enantiomer.]

20. (Amended) A [use] method according to [any preceding] claim 1, wherein said [medicament comprises] compound is administered in combination with a pharmaceutically acceptable carrier [and as active ingredient an effective amount of compound (I)].

21. (Amended) A [use] method according to claim 20, wherein said carrier comprises a cyclodextrin or an ether derivative thereof.

22. (Amended) A [use] method according to [any preceding] claim 20, wherein said carrier [the medicament] further comprises a buffer system, an isotonizing agent and water.

23. (Amended) [Use] A method according to [any of preceding] claim 1, wherein [the] said compound of formula (I) is administered in combination with one or more additional drugs useful in neuroprotection or in the treatment of cerebral ischaemia, central nervous system injury or eye diseases, the components being in the same formulation or in separate formulations for administration simultaneously or sequentially.

CHEMICAL COMPOUNDS - III

The present invention relates primarily to neuroprotection and to the treatment of stroke and other cerebrovascular disorders.

Stroke and other acute brain injuries are major causes of mortality and morbidity in the adult population. Stroke is the third highest cause of death in major industrialised countries and the commonest cause of permanent disability. Each year, in the US and Europe, approximately 1 million people suffer an acute stroke. Between 25% and 35% of these patients die within the first three weeks, and of the survivors 25% to 50% will be totally dependant on family or institutional care for the rest of their lives. The incidence of stroke increases with age, roughly doubling with each passing decade, with 30% of persons aged over 65 years being affected.

The statistics for stroke translate into an annual incidence of 0.1 to 0.2% in the US and Europe, with the world-wide market for stroke estimated to be worth $3 billion in 1995 and projected to rise to $10 billion in 2005. There is an unmet medical need for a cytoprotective therapy for stroke.

No effective neuroprotectant therapy is presently available for cerebrovascular disorders. The only therapy currently licensed for the treatment of ischaemic stroke is Genetech's thrombolytic recombinant tissue plasminogen activator (Activase®, rtPA; Alteplase). Activase is indicated for the management of acute ischaemic stroke in adults for improving neurological recovery and reducing the incidence of disability. Treatment with Activase should only be initiated within 3 hours after the onset of stroke symptoms, and after exclusion of intracranial haemorrhage by a cranial computerised tomography (CT) scan or other diagnostic imaging method sensitive for the presence of haemorrhage.

The mechanisms underlying the irreversible brain damage which occurs following ischaemia are complex. Many classes of compounds are currently under investigation as treatments for cerebrovascular disorders. Acute intervention with both cytoprotective (neuroprotective) and other thrombolytic agents is undergoing active investigation.

Cytoprotective neuroprotective therapy includes drugs that act to prevent cell death during ischaemia and reperfusion. These agents include calpain inhibitors, voltage-sensitive calcium- and sodium-channel antagonists, receptor-mediated calcium-channel antagonists [including *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) antagonists], glutamate-synthesis inhibitors, glutamate-release antagonists, γ-aminobenzoic acid (GABA) antagonists, 5-HT (serotonin) receptor agonists, gangliosides, antioxidants, growth factors, antiapoptotic agents, and antiadhesion molecules (Silver, B., Weber, J., Fisher, M., *Clin. Neuropharmacol.* **1996**, *19*, 101-128).

Excitotoxicity is a major determinant of neuronal death following the induction of cerebral ischaemia. Repetitive cell firing, persistent depolarisation and induction of supra-normal ionic flux across excitable membranes can initiate fatal cellular compromise *via* a variety of synergistic mechanisms during hypoxic excitotoxicity. Control of the state of excitability of neurons depends upon the net balance of excitatory and inhibitory influences acting on that neurone.

In general, the primary excitatory influence impinging on neurones is mediated by the glutamatergic system, whilst primary inhibition is frequently determined by GABAergic innervation, since the main endogenous inhibitory amino acid in mammalian brain is GABA. Thus increasing the inhibitory effect of GABAergic innervation, and decreasing the excitatory influence of glutamate, will reduce the net excitation of a neurone. Reducing excitation will reduce the consequences of energy depletion due to hypoxia and promote the ability of the neurone to survive hypoxic cerebral ischaemia.

Relatively few of the drugs currently under investigation as neuroprotectants for the treatment of stroke and other cerebrovascular disorders are modulators of the endogenous inhibitory amino acid, GABA.

One class of molecules which apparently possess neuroprotective properties is the GABA uptake inhibitors such as CI-966, which was shown to be effective in a gerbil ischaemia model utilising global cerebral ischaemia of 5 min. duration (Phillis, J.W., *Gen. Pharmacol.* **1995**, *26*, 1061-1064).

The benzodiazepine receptor agonist diazepam has been shown to possess some neuroprotective properties (Karle, J., Witt, M. R., Nielsen, M., *Brain Res.* **1997**, *765*, 21-29).

In rabbits with reversible spinal cord ischaemia, treatment with muscimol, a reference $GABA_A$ agonist, at 5 mg/kg significantly prolonged P_{50} time, where P_{50} represents the duration associated with 50% probability of resultant permanent paraplegia (Madden, K.P., *Stroke*, **1994**, *25*, 2271-2275).

Felbamate, an antiepileptic drug with *inter alia* GABA agonist properties, provided significant neuronal protection when administered both before and after ischaemia in all regions of the brain in the gerbil model of transient forebrain ischaemia. Protection was moderate when felbamate was used before ischaemia, but was highly significant when felbamate was given 30 min. after the insult. The structural protection with felbamate was very significant when used in the post-ischaemic period (Shuaib, A., Waqaar, T., Ijaz, M.S., Kanthan, R., Wishart, T., Howlett, W., *Brain Res.* **1996**, *727*, 65-70).

Piracetam is a derivative of GABA, and was the first commercially available nootropic drug. Although widely evaluated in the treatment of senile cognitive disorders and dyslexia, piracetam has also been assessed as a treatment for deficits associated with acute stroke. Data from a number of small, short term studies in patients treated within a few days of stroke suggest that piracetam is more effective than placebo for the treatment of functional deficits (Noble, S., Benfield, P., *CNS Drugs* **1998**, *9*, 497-511).

Some combination neuroprotectant therapies have been investigated in rodent ischaemia since the excitotoxic effects of glutamate can be blocked almost completely with GABA in cell culture, tissue slices, and in some animal models. On this basis a combination of muscimol and MK 801, an NMDA receptor antagonist, was investigated and shown to be effective (Lyden, P.D., Lonzo, L., *Stroke* **1994**, *25*, 189-196).

WO-A-99/25353 discloses the use of triazolo[4,3-b]pyridazine derivatives as benzodiazepine/$GABA_A$ modulators for the treatment of psychotic disorders and neurodegeneration.

WO-A-90/09174 discloses the use of the GABAergic agent Clomethiazole (chlormethiazole) in the prevention and/or treatment of neurodegeneration. Clomethiazole is thought to act through a GABAergic pathway, whereby it augments GABA's inhibitory effect on the CNS, giving the drug both hypnotic and neuroprotectant properties.

The clinical neuroprotectant profile of clomethiazole has been reviewed (Muckle, H., *IDrugs* **1999**, *2*, 184-193). A large-scale phase III trial has been completed in which clomethiazole was evaluated for its ability to reduce nerve damage in acute cerebrovascular ischaemia. A subgroup of patients who presented with large stroke, experienced a significant benefit. Of these (n = 545), 41% of treated patients were functionally independent after 90 days, compared to 30% of patients on placebo.

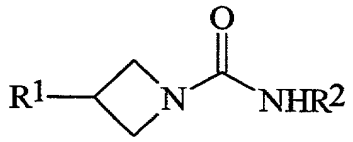
The effectiveness of this GABA modulator in rat (Snape, M.F., Baldwin, H.A., Cross, A.J., Green, A.R., *Neuroscience* **1993**, *53*, 837-844) and gerbil ischaemia (Cross, A.J., Jones, J.A., Baldwin, H.A., Green, A.R., *Br. J. Pharmacol.* **1991**, *104*, 406-411) has been demonstrated. The dose in the latter paradigm was 100 mg/kg, i.p.

Azetidine-1-carboxamides and the use of these compounds in the treatment of anxiety and all forms of epilepsy is described in International Patent Application No. PCT/GB99/00223.

There remains a medical need for new treatments for stroke and cerebrovascular disorders. The object of the present invention is to provide such treatments.

It has now been found that certain azetidine-1-carboxamides show unexpected neuroprotectant efficacy when compared to reference GABAergic agents. In particular, certain azetidine-1-carboxamides have been shown to potentiate the action of GABA in inhibiting neurones, and have also been shown to prevent the repetitive firing induced as a consequence of activation of glutamatergic mechanisms. Such compounds are found to be neuroprotective following acute cerebral ischaemia in rats and mice, and reduced ischaemia-induced CNS damage in *in vivo* models of focal ischaemia in both species.

According to the present invention, there is provided the use of a compound of formula (I)



(I)

wherein:

R^1 is aryl; and

R^2 is hydrogen or alkyl;

or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for neuroprotection in a subject or for the treatment of cerebral ischaemia, central nervous system injury or eye diseases.

Reference in the present specification to an "alkyl" group means a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenyl or alkynyl) hydrocarbyl radical. Where cyclic or acyclic the alkyl group is preferably C_1 to C_{12}, more preferably C_1 to C_8 (such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, isopentyl, hexyl, heptyl, octyl). It will be appreciated therefore that the term "alkyl" as used herein includes alkyl (branched or unbranched), alkenyl (branched or unbranched), alkynyl (branched or unbranched), cycloalkyl, cycloalkenyl and cycloalkynyl. In a preferred embodiment, a cyclic alkyl group is preferably C_3 to C_{12}, more preferably C_5 to C_8 and an acyclic alkyl group is preferably C_1 to C_{10}, more preferably C_1 to C_6, more preferably methyl, ethyl, propyl (n-propyl or isopropyl), butyl (n-butyl, isobutyl or tertiary-butyl) or pentyl (including n-pentyl and iso-pentyl), more preferably methyl.

Reference in the present specification to an "aryl" group means a mono or bicyclic aromatic group, such as phenyl or naphthyl.

The alkyl and aryl groups may be substituted or unsubstituted. In one embodiment, only the aryl group defined above as R_1 and the alkyl group defined above as R_2 may be substituted. Where substituted, there will generally be 1 to 3 substituents present, preferably 1 or 2 substituents. Substituents may include:

carbon containing groups such as

alkyl

aryl, arylalkyl (e.g. substituted and unsubstituted phenyl, substituted and unsubstituted benzyl);

halogen atoms and halogen containing groups such as

haloalkyl (e.g. trifluoromethyl);

oxygen containing groups such as

alcohols (e.g. hydroxy, hydroxyalkyl, (aryl)(hydroxy)alkyl),

ethers (e.g. alkoxy, alkoxyalkyl, aryloxyalkyl),

aldehydes (e.g. carboxaldehyde),

ketones (e.g. alkylcarbonyl, alkylcarbonylalkyl, arylcarbonyl, arylalkylcarbonyl, arylcarbonylalkyl),

acids (e.g. carboxy, carboxyalkyl),

acid derivatives such as esters

(e.g. alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl)

and amides

(e.g. aminocarbonyl, mono- or dialkylaminocarbonyl, aminocarbonylalkyl, mono- or dialkylaminocarbonylalkyl, arylaminocarbonyl);

nitrogen containing groups such as

amines (e.g. amino, mono- or dialkylamino, aminoalkyl, mono- or dialkylaminoalkyl),

azides,

nitriles (e.g. cyano, cyanoalkyl),

nitro;

sulphur containing groups such as

thiols, thioethers, sulphoxides and sulphones

(e.g. alkylthio, alkylsulfinyl, alkylsufonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, arylthio, arylsulfinyl, arylsulfonyl, arylthioalkyl, arylsulfinylalkyl, arylsulfonylalkyl); and

heterocyclic groups containing one or more, preferably one,

heteroatom,

(e.g. thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, piperidyl, piperazinyl, morpholinyl, thionaphthyl, benzofuranyl, isobenzofuryl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, isoindazolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolyl, isoquinolyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxadinyl, chromenyl, chromanyl, isochromanyl and carbolinyl).

Preferred substituents include alkyl, aryl, halo, or an halogen-containing group such as trifluoromethyl.

As used herein, the term "alkoxy" means alkyl-O- and "alkoyl" means alkyl-CO-.

As used herein, the term "halogen" means a fluorine, chlorine, bromine or iodine radical, preferably a fluorine or chlorine radical.

The compounds of formula (I) may exist in a number of diastereomeric and/or enantiomeric forms. Unless otherwise stated, reference in the present specification to "a compound of formula (I)" is a reference to all stereoisomeric forms of the compound and includes a reference to the unseparated stereoisomers in a mixture, racemic or non-racemic, and to each stereoisomer in its pure form.

In a preferred embodiment of the present invention, a compound of formula (I) is the (*R*)-enantiomer of the compound of formula (I), substantially free of its (*S*)-enantiomer.

In the compounds of formula (I), preferably R^1 is a substituted or unsubstituted aryl group selected from phenyl and naphthyl, more preferably R^1 is a substituted phenyl or naphthyl, more preferably R^1 is phenyl or naphthyl having 1 to 3 substituents and most preferably R^1 is

phenyl or naphthyl having 1 or 2 substituents. In a preferred embodiment of the invention, R^1 is a mono- or di-substituted phenyl group, preferably a mono-substituted phenyl group.

Where R^1 is napthyl, it is preferred that R^1 is 2-naphthyl.

The preferred substituent groups are selected from halo (preferably fluoro and chloro), trifluoromethyl and tertiary butyl, and more preferably from fluoro, chloro and trifluoromethyl.

Where R^1 is a phenyl having 1 substituent, the phenyl group is preferably para- or meta-substituted. Where R^1 is a phenyl having 2 substituents, the phenyl group is preferably 2,3-disubstituted, 2,4-disubstituted, 3,4-disubstituted or 3,5-disubstituted, preferably 3,4-disubstituted.

Where R^1 is disubstituted, it is preferred that R^1 is substituted by two halo groups, the same or different, or by one halo group and one trifluoromethyl group. More preferably, R^1 is dichloro-, difluoro-, chloro-fluoro- or fluoro-trifluoromethyl-substituted.

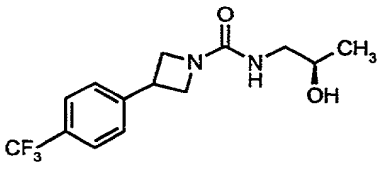
The R^1 groups are preferably selected from 4-chlorophenyl, 4-fluorophenyl, 4-(trifluoromethyl)phenyl, 3-(trifluoromethyl)phenyl, 3,4-difluorophenyl, 3,4-dichlorophenyl, 3-chloro-4-fluorophenyl, 4-chloro-3-fluorophenyl, 3-fluoro-4-(trifluoromethyl)phenyl, 4-fluoro-3-(trifluoromethyl)phenyl and 3-chloro-5-fluorophenyl.

In one embodiment of the present invention R^2 is alkyl, preferably selected from C_{1-8} alkyl, more preferably from alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl and unsubstituted saturated cyclic and acyclic hydrocarbyl, and more preferably from propyl, 2-propenyl, 2-propynyl and 2-hydroxypropyl.

Particularly preferred compounds are as follows:-

Chirality	R^1	R^2
-	4-Cl-C_6H_4	2-propenyl
-	4-F-C_6H_4	2-propenyl
-	4-F-C_6H_4	2-propynyl
R	4-F-C_6H_4	MeCH(OH)CH_2
-	4-Cl-C_6H_4	2-propynyl
R	4-Cl-C_6H_4	MeCH(OH)CH_2
S	4-F-C_6H_4	MeCH(OH)CH_2
S	4-CF_3-C_6H_4	MeCH(OH)CH_2
-	3-CF_3-C_6H_4	2-propynyl
-	4-CF_3-C_6H_4	2-propynyl
R	4-CF_3-C_6H_4	MeCH(OH)CH_2
-	4-CF_3-C_6H_4	H

In a preferred embodiment of the present invention, the compound of formula (I) is 3-(4-(trifluoromethyl)phenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide **(Ia)** or a pharmaceutically acceptable salt or prodrug thereof. In a particularly preferred embodiment of the present invention, the compound of formula (I) is the (*R*)-enantiomer of 3-(4-(trifluoromethyl)phenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide **(Ib)**, substantially free of its (*S*)-enantiomer, or a pharmaceutically acceptable salt or prodrug thereof.



Compound Ib

According to a further aspect of the present invention there is provided a method of neuroprotection comprising administration to a subject in need of such treatment an effective dose of the compound of formula (I), or a pharmaceutically acceptable salt or prodrug thereof.

According to a further aspect of the present invention there is provided a method of treatment of cerebral ischaemia, central nervous system injury or eye diseases comprising administration to a subject in need of such treatment an effective dose of the compound of formula (I), or a pharmaceutically acceptable salt or prodrug thereof.

The present invention may be employed in respect of a human or animal subject, more preferably a mammal, more preferably a human subject.

As used herein, the term "treatment" as used herein includes prophylactic treatment.

As used herein, the term "prodrug" means any pharmaceutically acceptable prodrug of the compound of formula (I). For example, the compound of formula (I) may be prepared in a prodrug form wherein a free –OH group is derivatised (for example, via an ester, amide or phosphate bond) with a suitable group (the group may contain, for example, an alkyl, aryl, phosphate, sugar, amine, glycol, sulfonate or acid function) which is suitably labile so as it will be removed / cleaved (eg. by hydrolysis) to reveal the compound of formula (I) sometime after administration or when exposed to the desired biological environment.

As used herein, the term "pharmaceutically acceptable salt" means any pharmaceutically acceptable salt of the compound of formula (I). Salts may be prepared from pharmaceutically acceptable non-toxic acids and bases including inorganic and organic acids and bases. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, dichloroacetic, furnaric, gluconic, glutamic, hippuric, hydrobromic, hydrochloric, isethionic,

lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, oxalic, p-toluenesulfonic and the like. Particularly preferred are hydrochloric, hydrobromic, phosphoric, sulfuric and methanesulfonic acids, and most particularly preferred is the methanesulfonate salt. Acceptable base salts include alkali metal (e.g. sodium, potassium), alkaline earth metal (e.g. calcium, magnesium) and aluminium salts.

As used herein, the term "substantially free of its (*S*)-enantiomer" means that the medicament or therapeutic composition comprising the compound of formula (I) used according to the present invention contains a greater proportion of the (*R*)-enantiomer of the compound of formula (I) in relation to the (*S*)-enantiomer of the compound of formula (I). In a preferred embodiment of the present invention the term "substantially free of its (*S*)-enantiomer", as used herein, means that the composition contains at least 90 % by weight of the (*R*)-enantiomer and 10 % by weight or less of the (*S*)-enantiomer. In a further preferred embodiment, the term "substantially free of its (*S*)-enantiomer" means that the composition contains at least 99 % by weight of the (*R*)-enantiomer and 1 % or less of the (*S*)-enantiomer. In another preferred embodiment, the term "substantially free of its (*S*)-enantiomer" means that the composition contains 100 % by weight of the (*R*)-enantiomer. The above percentages are based on the total amount of compound of formula (I) present in the medicament or therapeutic composition used according to the present invention.

The diseases, disorders and medical treatments/procedures to which the present invention is directed are:

Cerebral Ischaemia,

including transient ischaemic attack, stroke (thrombotic stroke, ischaemic stroke, embolic stroke, haemorrhagic stroke, lacunar stroke), subarachnoid haemorrhage, cerebral vasospasm, neuroprotection for stroke, peri-natal asphyxia, drowning, carbon monoxide poisoning, cardiac arrest and subdural haematoma;

Central Nervous System Injury,

including traumatic brain injury, neurosurgery (surgical trauma), neuroprotection for head injury, raised intracranial pressure, cerebral oedema, hydrocephalus and spinal cord injury; and

Eye Diseases,
including drug-induced optic neuritis, cataract, diabetic neuropathy, ischaemic retinopathy, retinal haemorrhage, retinitis pigmentosa, acute glaucoma, chronic glaucoma, macular degeneration, retinal artery occlusion and retinitis.

Additionally, the compound of formula (I) may also be used to potentiate the effects of other treatments, for example to potentiate the neuroprotective effects of brain derived nerve growth factor.

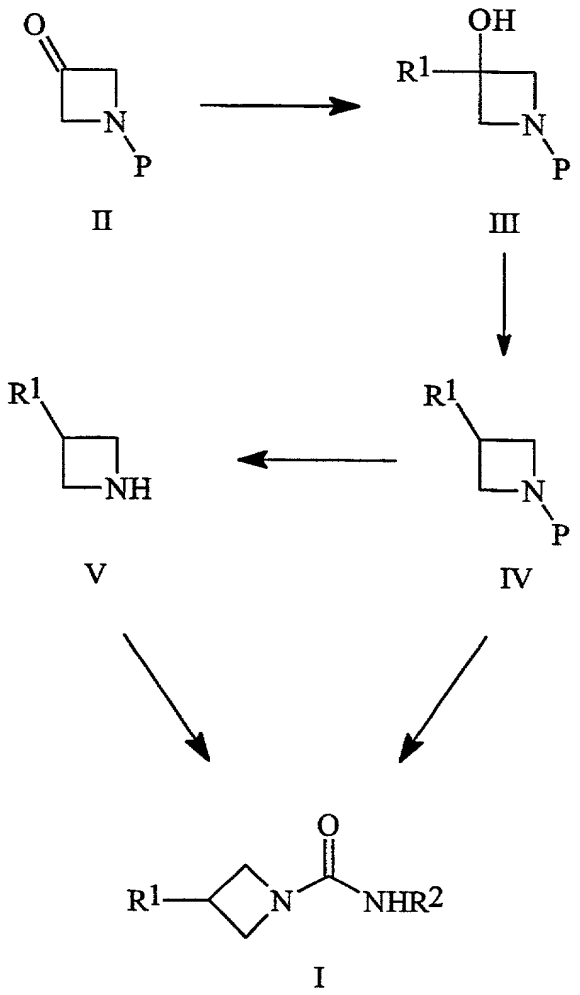
The invention is particularly directed to the treatment of cerebral ischaemia and central nervous system injury. The invention is also particularly directed to the treatment of post-asphyxial brain damage in new-born subjects.

The compound of formula (I) may be used in combination with one or more additional drugs useful in the treatment of the disorders mentioned above, the components being in the same formulation or in separate formulations for administration simultaneously or sequentially.

Compounds of formula (I) may be prepared according to the reaction scheme (where P is a nitrogen protecting group). R^1 and R^2 are as previously defined. The 3-aryl-3-azetidinol (III) may be formed by treatment of the ketone (II) with an organometallic reagent such as an aryllithium or an arylmagnesium halide. Removal of the hydroxyl group to give the 3-arylazetidine (IV) may be effected by several methods including, for example, catalytic hydrogenolysis; treatment with lithium or sodium and ammonia; conversion to the xanthate by treatment with carbon disulphide, methyl iodide and base, followed by tin-mediated reduction; and conversion to the 3-aryl-3-chloroazetidine analogue using an alkylsulfonyl chloride and a base, followed by a reductive dechlorination using sodium, lithium or nickel. Formation of the azetidine (V) is achieved by reaction of (IV) with a suitable nitrogen deprotection agent. For example, if P is a diphenylmethyl group, then deprotection may be carried out by either catalytic transfer hydrogenation (e.g. ammonium formate and palladium catalyst) or by treatment with 1-chloroethyl chloroformate followed by methanol. The urea (I) is formed by reaction of azetidine (V) with an N-alkylisocyanate or an N-alkylcarbamoyl chloride and a base such as triethylamine or potassium carbonate. Alternatively, the urea may

be prepared directly from the azetidine (IV) without isolation of an intermediate such as the secondary amine (V). For example, when P is a diphenylmethyl group, azetidine (IV) may be treated with phosgene followed by amine R^2NH_2 to give urea (I) directly.

Reaction Scheme



The invention further provides a pharmaceutical composition comprising an effective amount of the compound of formula (I) in combination with a pharmaceutically acceptable carrier or excipient and a method of making such a composition comprising combining an effective amount of the compound of formula (I) with a pharmaceutically acceptable carrier or excipient.

To further increase efficacy, the composition may contain components such as dextrans or cyclodextrins or ether derivatives thereof, which aid stability and dispersion, and decrease metabolism of the active ingredient.

For compositions in which the pharmaceutically acceptable carrier comprises a cyclodextrin or an ether derivative thereof, the active ingredient is intimately mixed with an aqueous solution of the cyclodextrin or ether derivative thereof, with optional addition of further pharmaceutically acceptable ingredients before, during or after said mixing. The thus obtained solution is optionally lyophilized, and the lyophilized residue is optionally reconstituted with water.

In an embodiment of the present invention, the composition further comprises a buffer system, an isotonizing agent and water.

Compounds of formula (I) may be administered in a form suitable for oral use, for example a tablet, capsule, aqueous or oily solution, suspension or emulsion; for topical use including transmucosal and transdermal use, for example a cream, ointment, gel, aqueous or oil solution or suspension, salve, patch or plaster; for nasal use, for a example a snuff, nasal spray or nasal drops; for vaginal or rectal use, for example a suppository; for administration by inhalation, for example a finely divided powder or a liquid aerosol; for sub-lingual or buccal use, for example a tablet or capsule; or for parenteral use (including intravenous, subcutaneous, intramuscular, intravascular or infusion), for example a sterile aqueous or oil solution or suspension. In general the above compositions may be prepared in a conventional manner using conventional excipients, using standard techniques well known to those skilled in the art of pharmacy. Preferably, the compound is administered orally.

For oral administration, the compounds of formula (I) will generally be provided in the form of tablets or capsules or as an aqueous solution or suspension.

Tablets for oral use may include the active ingredient mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose,

while corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin, while the lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract.

Capsules for oral use include hard gelatin capsules in which the active ingredient is mixed with a solid diluent, and soft gelatin capsules wherein the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

For intramuscular, intraperitoneal, subcutaneous and intravenous use, the compounds of formula (I) will generally be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride. Aqueous suspensions may include suspending agents such as cellulose derivatives, sodium alginate, polyvinyl-pyrrolidone and gum tragacanth, and a wetting agent such as lecithin. Suitable preservatives for aqueous suspensions include ethyl and n-propyl p-hydroxybenzoate.

It will be appreciated that the dosage levels used may vary over quite a wide range depending upon the compound used, the severity of the symptoms exhibited by the patient and the patient's body weight.

The invention will now be described in detail with reference to the following examples. It will be appreciated that the examples are intended to illustrate and not to limit the scope of the present invention.

EXAMPLES

Synthetic Examples

1-(Diphenylmethyl)-3-azetidinol (2)

The compound (2) was prepared according to the method of Anderson and Lok (*J. Org. Chem.* **1972**, *37*, 3953, the disclosure of which is incorporated herein by reference), m.p. 111-112 °C (lit. m.p. 113 °C).

1-Diphenylmethyl-3-azetidinone (3)

Dimethyl sulfoxide (0.36 mL, 5 mmol) was added dropwise to a stirred solution of oxalyl chloride (0.40 mL, 4.6 mmol) in dichloromethane (20 mL) at -78 °C under an argon atmosphere. The mixture was stirred for 10 minutes then a solution of 1-(diphenylmethyl)-3-azetidinol (1.0 g, 4.2 mmol) in dichloromethane (20 mL) was added dropwise. The mixture was warmed to -50 °C and stirred for 30 minutes. Triethylamine (2.9 mL, 21 mmol) was added and the mixture warmed to room temperature. After 1 hour, water (50 mL) was added and the mixture extracted with dichloromethane (4 x 50 mL). The combined organic extracts were washed (brine), dried (Na_2SO_4) and concentrated *in vacuo* to give 1-diphenylmethyl-3-azetidinone (3) as a pale yellow crystalline solid (1.0 g, 99 %) (lit. (S.S. Chatterjee and A. Shoeb, *Synthesis*, 1973,153) m.p. 82°C).

3-(4-Chlorophenyl)-1-(diphenylmethyl)-3-azetidinol (4)

To a stirred solution of 4-chlorophenylmagnesium bromide (9.1 mL, 1.0M in diethyl ether) in diethyl ether (80 mL) at -78 °C under an argon atmosphere was added compound 3 (1.8 g, 7.6 mmol) in diethyl ether (50 mL) dropwise over 20 minutes. The reaction mixture was stirred at -78 °C for 2 hours, then slowly warmed to room temperature with stirring over 18 hours. The reaction mixture was then partitioned between aqueous ammonium acetate solution (50 mL) and diethyl ether (50 mL). The aqueous layer was extracted with diethyl ether (3 x 50 mL) and the combined organic extracts were washed (water, brine), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product as a pale yellow viscous oil in quantitative yield. A sample purified for analysis by column chromatography on silica gel using 15-30% ethyl acetate-hexane as eluent and subsequent crystallisation from hexane gave 3-(4-

chlorophenyl)-1-(diphenylmethyl)-3-azetidinol (4), m.p. 108°C. Found: C, 75.42; H, 5.79; N, 3.98. $C_{22}H_{20}ClNO$ requires C, 75.53; H, 5.76; N, 4.00%.

O-(3-(3-(4-Chlorophenyl)-1-diphenylmethyl))azetidinyl)-S-methyldithiocarbonate (5)

To a stirred suspension of sodium hydride (0.4 g of a 60% suspension in mineral oil, 10.4 mmol) (prewashed with hexane) in THF (80 mL) was added dropwise a solution of compound 4 (1.7 g, 4.9 mmol) in THF (80 mL). The mixture was stirred for 3 hours then carbon disulphide (17.6 mL, 0.29 mol) and methyl iodide (6.1 mL, 0.1 mol) were added dropwise. The mixture was stirred at room temperature for 15 hours and then heated to 50 °C while the solvent was removed in a stream of argon. When the volume of the mixture was reduced by half, the mixture was concentrated *in vacuo* to an approximate volume of 20 mL and then partitioned between water and diethyl ether. The organic layer was washed with water and then brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was crystallised from hexane to give *O*-(3-(3-(4-chlorophenyl)-1-diphenylmethyl))azetidinyl)-*S*-methyldithiocarbonate (5) (2.06g, 96%).

3-(4-Chlorophenyl)-1-(diphenylmethyl)azetidine (6)

To a stirred solution of tributyltin hydride (1.8 mL, 6.9 mmol) in dry toluene (40 mL) at reflux under an argon atmosphere was added dropwise, over 1 hour, a solution of compound 5 (2.0 g, 4.6 mmol) in toluene (40 mL). The mixture was heated under reflux for a further 2 hours then was concentrated *in vacuo*. The residue obtained was purified by flash column chromatography on silica gel using hexane and then 10% ethyl acetate-hexane as eluent. The product was recrystallised twice from hexane to give 3-(4-chlorophenyl)-1-(diphenylmethyl)azetidine (6) (0.4 g, 34%) m.p. 82 °C. Found: C, 78.94; H, 6.06; N, 4.14. $C_{22}H_{20}ClN$ requires C, 79.15; H, 6.04; N, 4.20%.

3-(4-Chlorophenyl)azetidine (7)

To a solution of compound 6 (0.36 g, 1.1 mmol) in 1,2-dichloroethane (10 mL) containing proton sponge (0.02 g), cooled in an ice-water bath under an argon atmosphere, was added

dropwise 1-chloroethyl chloroformate (0.3 mL, 3.1 mmol). The resultant solution was boiled at reflux for 4 hours, cooled and was concentrated *in vacuo*. The residue obtained was mixed with methanol (10 mL) and heated under reflux for 2 hours, then cooled and concentrated *in vacuo* to give the hydrochloride salt of 3-(4-chlorophenyl)azetidine (7) which was used without further purification.

Example 1. 3-(4-Chlorophenyl)-*N*-(2-propenyl)azetidine-1-carboxamide (8)

To the hydrochloride salt of 3-(4-chlorophenyl)azetidine (7) (approximately 1.1 mmol) in ethanol (10 mL) stirred at 0°C was added sequentially and dropwise allyl isocyanate (0.15 mL, 1.7 mmol) followed by triethylamine (0.3 mL, 2.2 mmol). After 20 minutes the reaction mixture was partitioned between aqueous ammonium chloride and ether. The organic layer was washed (water and then brine), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a crude product. The product obtained was purified by column chromatography on silica gel using 20% ethyl acetate-hexane as eluent to give 3-(4-chlorophenyl)-*N*-(2-propenyl)azetidine-1-carboxamide (8) which was recrystallised from cyclohexane/toluene (0.16 g, 61%), m.p. 112 °C. Found: C, 62.20; H, 6.23; N, 11.40. $C_{13}H_{15}ClN_2O$ requires C, 62.28; H, 6.03; N, 11.17%.

3-(4-tert-Butylphenyl)-1-diphenylmethyl-3-azetidinol (9)

To a stirred solution of 4-tert-butylphenylmagnesium bromide (11.5 mL, 2.0M (Et_2O)) in toluene (50 mL) at -78°C under argon, was added, dropwise, a solution of 1-diphenylmethyl-3-azetidinone (3) (5.0 g) in toluene (100 mL) over 30 minutes. The mixture was stirred for 4 hours at -78°C then warmed to room temperature and partitioned between aqueous ammonium chloride solution (50 mL) and diethyl ether (3 x 50 mL). The combined organic fractions were washed (water, brine), dried (Na_2SO_4) and concentrated in vacuo. Recrystallisation from cyclohexane gave 3-(4-tert-butylphenyl)-1-diphenylmethyl-3-azetidinol (9) (6.23 g), m.p. 168-169°C (cyclohexane). Found: C. 83.68; H, 7.97; N, 3.72. $C_{26}H_{29}NO$ requires C, 84.06; H, 7.87; N, 3.77%.

3-(4-tert-Butylphenyl)-3-chloro-1-(diphenylmethyl)azetidine (10)

To a stirred solution of compound (9) (6.23 g) and N,N-diisopropylethylamine (3.5 mL) in dichloromethane (100 mL) at 0°C was added, dropwise, methanesulfonyl chloride (1.4 mL). The mixture was stirred at 0°C for 18 hrs, then washed (water, brine), dried (Na_2SO_4) and concentrated in vacuo. The crude product was recrystallised from hexane to give 3-(4-tert-butylphenyl)-3-chloro-1-(diphenylmethyl)azetidine (10) (4.73 g) m.p. 145°C (hexane). Found: C, 80.30; H, 7.05; N, 3.64. $C_{26}H_{28}ClN$ requires C, 80.08; H, 7.24; N, 3.59%.

3-(4-tert-Butylphenyl)-1-(diphenylmethyl)azetidine (11)

To a stirred suspension of Raney Nickel (8.6 g, wet slurry) in tertiary butanol (50 mL) and toluene (50 mL) was added a solution of 3-(4-tert-butylphenyl)-3-chloro-1-(diphenylmethyl)azetidine (10) (4.73 g) in toluene (10 mL). The mixture was heated to 80°C for 6 hours, cooled to room temperature and filtered through kieselguhr. The filtrate was concentrated in vacuo and partitioned between diethyl ether (3 x 50 mL) and aqueous potassium carbonate solution (50 mL). The combined organic extracts were washed (water, brine), dried (Na_2SO_4), concentrated in vacuo and purified by flash column chromatography (10% ethyl acetate/hexane) on silica. Recrystallisation from methanol gave 3-(4-tert-butylphenyl)-1-(diphenylmethyl)azetidine (11) (3.40 g), m.p. 95°C (methanol). Found: C, 87.84; H, 8.17; N, 3.92. $C_{26}H_{29}N$ requires C, 87.84; H, 8.22; N, 3.94%.

Example 2. 3-(4-tert-Butylphenyl)-*N*-(2-propenyl)azetidine-1-carboxamide (12)

To a stirred solution of 3-(4-tert-butylphenyl)-1-(diphenylmethyl)azetidine (11) (1.0 g) in dichloromethane (10 mL) at 0°C was added dropwise a solution of 20% phosgene in toluene (2.5 mL). The mixture was stirred for 90 minutes then concentrated in vacuo. To the concentrate was added dichloromethane (10 mL) and to this solution at 0°C was added, dropwise, with stirring, allylamine (0.8 mL). The mixture was stirred for 18 hrs at room temperature, diluted with dichloromethane (30 mL), washed (water, brine), dried (Na_2SO_4), concentrated in vacuo and purified by flash column chromatography (50% ethyl acetate-hexane) to give 3-(4-tert-butylphenyl)-*N*-(2-propenyl)azetidine-1-carboxamide (12) (0.21 g), m.p. 98-99°C (diisopropyl ether). Found: C, 74.95; H, 8.97; N, 10.25. $C_{17}H_{24}N_2O$ requires C, 74.96; H, 8.88; N, 10.28%.

Example 3. 3-(4-tert-Butylphenyl)-*N*-(2-propynyl)azetidine-1-carboxamide (13)

To a stirred solution of 3-(4-tert-butylphenyl)-1-(diphenylmethyl)azetidine (11) (0.5 g) in dichloromethane (5 mL) at 0°C was added dropwise a solution of 20% phosgene in toluene (0.8 mL). The mixture was stirred for 90 minutes then concentrated in vacuo. To the concentrate was added dichloromethane (5 mL) and to this solution at 0°C was added dropwise with stirring propargylamine (0.24 mL). The mixture was stirred for 18 hrs at room temperature, diluted with dichloromethane (20 mL), washed (water, brine), dried (Na_2SO_4) and concentrated in vacuo. Trituration with diethyl ether (2 mL) gave 3-(4-tert-butylphenyl)-*N*-(2-propynyl)azetidine-1-carboxamide (13) (0.14 g), m.p. 141°C (diethyl ether). Found: C, 75.40; H, 8.19; N, 10.38. $C_{17}H_{22}N_2O$ requires C, 75.52; H, 8.20; N, 10.36%.

Example 4. (R)-3-(4-tert-Butylphenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide (14)

To a stirred solution of 3-(4-tert-butylphenyl)-1-(diphenylmethyl)azetidine (11) (0.50 g) in dichloromethane (5 mL) at 0°C was added dropwise a solution of 20% phosgene in toluene (0.8 mL). The mixture was stirred for 90 minutes then concentrated in vacuo. To the concentrate was added dichloromethane (5 mL) and to this solution at 0°C was added dropwise with stirring (R)-1-amino-2-propanol (0.25 mL). The mixture was stirred for 18 hrs at room temperature, diluted with dichloromethane (20 mL), washed (water, brine), dried (Na_2SO_4) concentrated in vacuo and purified by flash column chromatography (10% methanol-ethyl acetate) to give (R)-3-(4-tert-butylphenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide (14) (0.35 g), m.p. 96-97°C (diisopropyl ether). Found: C, 69.59; H, 8.74; N, 9.23. $C_{17}H_{26}N_2O$ requires C, 70.31; H, 9.02; N, 9.64%.

3-(4-Fluorophenyl)-1-diphenylmethyl-3-azetidinol (15)

To a stirred solution of 4-fluorophenylmagnesium bromide (7.0 mL, 1.0M (Et_2O)) in toluene (20 mL) at -78°C under argon, was added, dropwise, a solution of 1-diphenylmethyl-3-

azetidinone (3) (1.4 g) in toluene (30 mL) over 30 minutes. The mixture was stirred for 4 hours at -78°C then warmed to room temperature and partitioned between aqueous ammonium chloride solution (50 mL) and diethyl ether (3 x 20 mL). The combined organic fractions were washed (water, brine), dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography (20% ethyl acetate, hexane) gave 3-(4-fluorophenyl)-1-diphenylmethyl-3-azetidinol (15) (1.82 g). To a stirred solution of the free base (1.82 g) in ether (5 mL) was added dropwise a solution of oxalic acid (0.49 g) in acetone (1 mL). The mixture was stirred for 5 minutes then filtered to give the oxalate salt hemihydrate (2.23 g), m.p. 75°C (acetone). Found: C, 66.71; H, 5.34; N, 3.04. $C_{24}H_{22}FNO_5.0.5H_2O$ requires C, 66.67; H, 5.32; N, 3.17%.

3-(4-Fluorophenyl)-3-chloro-1-(diphenylmethyl)azetidine (16)

To a stirred solution of 3-(4-fluorophenyl)-1-diphenylmethyl-3-azetidinol (15) (4.0 g) and N,N-diisopropylethylamine (3.2 mL) in dichloromethane (100 mL) at 0°C was added, dropwise, methanesulfonyl chloride (1.25 mL). The mixture was stirred at 0°C for 18 hrs, then washed (water, brine) and dried (Na_2SO_4) and concentrated in vacuo. The crude product was recrystallised from hexane to give 3-(4-fluorophenyl)-3-chloro-1-(diphenylmethyl)azetidine (16) (2.2 g), m.p. 108-109°C (hexane). Found: C, 75.13; H, 5.46; N, 3.93. $C_{22}H_{19}ClFN$ requires C, 75.10; H, 5.44; N, 3.98%.

3-(4-Fluorophenyl)-1-(diphenylmethyl)azetidine (17)

To a stirred suspension of Raney Nickel (2.0 g, wet slurry) in tertiary butanol (10 mL) and toluene (50 mL) was added a solution of 3-(4-fluorophenyl)-3-chloro-1-(diphenylmethyl)azetidine (16) (1.9 g) in toluene (20 mL). The mixture was heated to 80°C for 6 hours, cooled and filtered through kieselguhr. The filtrate was concentrated in vacuo and partitioned between diethyl ether (3 x 30 mL) and aqueous potassium carbonate solution (50 mL). The combined organic extracts were washed (water, brine), dried (Na_2SO_4), and concentrated in vacuo. Recrystallisation from diisopropyl ether gave 3-(4-fluorophenyl)-1-(diphenylmethyl)azetidine (17) (1.5 g), m.p. 65-66°C (diisopropyl ether). Found: C, 83.25; H, 6.35; N, 4.41. $C_{22}H_{20}FN$ requires C, 83.25; H, 6.35; N, 4.41%.

Example 5. 3-(4-Fluorophenyl)-*N*-(2-propenyl)azetidine-1-carboxamide (18)

To a stirred solution of 3-(4-fluorophenyl)-*N*-(diphenylmethyl)azetidine (17) (0.67 g) in dichloromethane (5 mL) at 0°C was added dropwise a solution of 20% phosgene in toluene (2.5 mL). The mixture was stirred for 90 minutes then concentrated in vacuo. To the concentrate was added dichloromethane (5 mL) and to this solution at 0°C was added, dropwise, with stirring, allylamine (0.5 mL). The mixture was stirred for 18 hrs at room temperature, diluted with dichloromethane (20 mL), washed (water, brine), dried (Na_2SO_4) and concentrated in vacuo. Recrystallisation from diisopropyl ether gave 3-(4-fluorophenyl)-*N*-(2-propenyl)azetidine-1-carboxamide (18) (0.30g), m.p. 119-120°C (diisopropyl ether). Found: C, 66.61; H, 6.37; N, 11.74. $C_{13}H_{15}FN_2O$ requires C, 66.65; H, 6.45; N, 11.95%.

Example 6. 3-(4-Fluorophenyl)-*N*-(2-propynyl)azetidine-1-carboxamide (19)

To a stirred solution of 3-(4-fluorophenyl)-1-(diphenylmethyl)azetidine (17) (0.38 g) in dichloromethane (5 mL) at 0°C was added dropwise a solution of 20% phosgene in toluene (1.4 mL). The mixture was stirred for 90 minutes then concentrated in vacuo. To the concentrate was added dichloromethane (5 mL) and to this solution at 0°C was added, dropwise, with stirring propargylamine (0.3 mL). The mixture was stirred for 18 hrs at room temperature, diluted with dichloromethane (20 mL), washed (water, brine), dried (Na_2SO_4) and concentrated in vacuo. The crude material was purified by flash column chromatography (50% ethyl acetate hexane) and then crystallised from diisopropyl ether to give 3-(4-fluorophenyl)-*N*-(2-propynyl)azetidine-1-carboxamide (19) (0.14g), m.p. 141°C (diisopropyl ether). Found: C, 67.32; H, 5.65; N, 11.93. $C_{13}H_{13}FN_2O$ requires C, 67.23; H, 5.64; N, 12.06%.

Example 7. (R)-3-(4-Fluorophenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide (20)

To a stirred solution of 3-(4-fluorophenyl)-1-(diphenylmethyl)azetidine (17) (0.35 g) in dichloromethane (5 mL) at 0°C was added dropwise a solution of 20% phosgene in toluene (1.2 mL). The mixture was stirred for 90 minutes then concentrated in vacuo. To the concentrate was added dichloromethane (5 mL) and to this solution at 0°C was added dropwise with stirring (R)-1-amino-2-propanol (0.2 mL). The mixture was stirred for 18 hrs

at room temperature,diluted with dichloromethane (20 mL), washed (water, brine), dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by flash column chromatography (10% methanol-ethyl acetate) to give (R)-3-(4-fluorophenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide (20) (0.21g), m.p. 104-105 °C (toluene/ethanol). Found: C, 61.93; H, 6.97; N, 10.9. $C_{13}H_{17}FN_2O_2$ requires C, 61.89; H, 6.79; N, 11.10%.

Example 8. (3-(4-Chlorophenyl)-*N*-(2-propynyl)azetidine-1-carboxamide (21)

This compound was prepared from 3-(4-chlorophenyl-1-(diphenylmethyl)azetidine (6) and propargylamine using the procedure outlined in Example 3, m.p. 160 °C (diethyl ether). Found C, 62.85; H, 5.38; N, 10.89 $C_{13}H_{13}ClN_2O$ requires C, 62.78; H, 5.27; N, 11.26%.

Example 9. (R)-3-(4-Chlorophenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide (22)

This compound was prepared from compound (6) and (R)-1-amino-2-propanol using the procedure outlined in Example 4, m.p. 92-93 °C (diethyl ether-toluene). Found: C, 58.97; H, 6.38; N, 9.96. $C_{13}H_{17}ClN_2O_2.0.2PhCH_3$, requires C, 60.23; H, 6.48; N, 9.76%.

Example 10: (*S*)-3-(4-Fluorophenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide (23)

This compound was prepared from compound (17) and (*S*)-1-amino-2-propanol using the procedure described for compound (20). m.p. 102-104°C. Found: C, 61.94; H, 6.72; N, 11.1. $C_{13}H_{17}FN_2O_2$ requires C, 61.89; H, 6.79; N, 11.10%.

3-(3,4-Dichlorophenyl)-1-(diphenylmethyl)azetidin-3-ol (24)

This compound was prepared from compound (3) and 3,4-dichlorophenylmagnesium bromide using the procedure described for compound (4).

3-(3,4-Dichlorophenyl)-3-chloro-1-(diphenylmethyl)azetidine (25)

This compound was prepared from compound (24) using the procedure described for compound (10).

3-(3,4-Dichlorophenyl)-1-(diphenylmethyl)azetidine (26)

This compound was prepared from compound (25) using the procedure described from compound (11).

Example 11. 3-(3,4-Dichlorophenyl)-*N*-(2-propynyl)azetidine carboxamide (27)

This compound was prepared from compound (26) and propargylamine using the procedure described for compound (12). m.p. 105.5-107.5°C.

Example 12. (R)-3-(3,4-Dichlorophenyl)-*N*-(2-hydroxypropyl)azetidine carboxamide (28)

This compound was prepared from compound (26) and (*R*)-1-amino-2-propanol using the procedure described for compound (12). m.p. 123-125°C. Found: C, 51.58; H, 5.33; N, 9.26. $C_{13}H_{16}Cl_2N_2O_2$ requires C, 51.50; H, 5.32; N, 9.24%.

Example 13. (S)-3-(3,4-Dichlorophenyl)-*N*-(2-hydroxypropyl)azetidine carboxamide (29)

This compound was prepared from compound (26) and (*S*)-1-amino-2-propanol using the procedure described for compound (12). m.p. 123-125°C. Found: C, 51.47; H, 5.30; N, 9.18. $C_{13}H_{16}Cl_2N_2O_2$ requires C, 51.50; H, 5.32; N, 9.24%.

3-(4-(Trifluoromethyl)phenyl)-1-(diphenylmethyl)azetidin-3-ol (30)

This compound was prepared from compound (3) and 4-(trifluoromethyl)phenylmagnesium bromide using the procedure described for compound (4).

3-Chloro-3-(4-(trifluoromethyl)phenyl)-(diphenylmethyl)azetidine (31)

This compound was prepared from compound (30) using the procedure described for compound (10).

3-(4-(Trifluoromethyl)phenyl)-1-(diphenylmethyl)azetidine (32)

This compound was prepared from compound (31) using the procedure described for compound (11).

Example 14. (R)-3-(4-(Trifluoromethyl)phenyl)-*N*-(2-hydroxypropyl)azetidine carboxamide (33)

This compound was prepared from compound (32) and (R)-1-amino-2-propanol using the procedure described for compound (12). m.p. 107-108°C. Found: C, 54.78; H, 5.75; N, 9.01. $C_{14}H_{17}F_3N_2O_2.0.25\ H_2O$ requires C, 54.81; H, 5.71, N, 9.13%.

Example 15. (S)-3-(4-(Trifluoromethyl)phenyl)-*N*-(2-hydroxypropyl)azetidine carboxamide (34)

This compound was prepared from compound (32) and (S)-1-amino-2-propanol using the procedure described for compound (12). m.p. 107-108°C. Found: C, 54.75; H, 5.68; N, 9.09. $C_{14}H_{17}F_3N_2O_2.0.25\ H_2O$ requires C, 54.81; H, 5.71; N, 9.13%.

Example 16. 3-(4-(Trifluoromethyl)phenyl)-*N*-(2-propynyl)azetidine-1-carboxamide (35)

This product was prepared from compound (32) and propargylamine using the procedure described for compound (12). m.p. 151-155°C.

3-(3-(Trifluoromethyl)phenyl)-1-(diphenylmethyl)azetidin-3-ol (36)

This compound was prepared from compound (3) and 3-(trifluoromethyl)phenylmagnesium bromide using the procedure described for compound (4).

3-Chloro-3-(3-(trifluoromethyl)phenyl)-(diphenylmethyl)azetidine (37)

This compound was prepared from compound (32) using the procedure described for compound (10).

3-(3-(Trifluoromethyl)phenyl)-1-(diphenylmethyl)azetidine (38)

This compound was prepared compound (37) using the procedure described for compound (11).

Example 17. (R)-3-(3-(Trifluoromethyl)phenyl)-*N*-(2-hydroxypropyl)azetidine carboxamide (39)

This compound was prepared from compound (38) and (R)-1-amino-2-propanol using the procedure described for compound (12). m.p. 81-82°C.

Example 18. (S)-3-(3-(Trifluoromethyl)phenyl)-*N*-(-2-hydroxypropyl)azetidine carboxamide (40)

This compound was prepared from compound (38) and (S)-1-amino-2-propanol using the procedure described for compound (12). m.p. 80-82°C.

Example 19. 3-(3-(Trifluoromethyl)phenyl)-*N*-(2-propynyl)azetidine-1-carboxamide (41)

This product was prepared from compound (38) and propargylamine using the procedure described for compound (12). m.p. 121°C.

Example 20. 3-(4-(Trifluoromethyl)phenyl)-N-azetidine-1-carboxamide (42)

To a solution of 3-(4-(Trifluoromethyl)phenyl)-1-(diphenylmethyl)azetidine (32) (8.2 mmol) in dichloromethane (20 mL) at 0°C, was added a solution of phosgene (1.75M in toluene, 10.2 mmol). The reaction mixture was stirred at room temperature for 90 minutes, concentrated *in vacuo*, then redissolved in THF (25 mL), cooled to 0°C and treated with ammonium hydroxide (12.5 mL). The reaction was stirred for 16 h, then water (80 mL) and ethyl acetate (100 mL) were added and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 100 mL), combined organic layers washed with brine (60 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was triturated using ethyl acetate (60 mL) to a solid (1.64 g, 81%), mp. 207.5-208.5-°C (ethyl acetate). Found: C, 54.51; H, 4.59; N, 11.41. $C_{14}H_{17}ClN_2O_2$ requires: C, 54.10; H, 4.54; N, 11.47.

Examples 21 to 84 – See Table 1

These products were prepared using the procedure described for compound 12.

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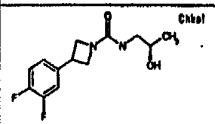
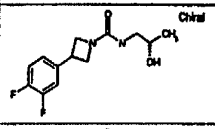
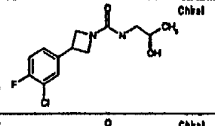
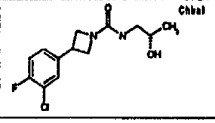
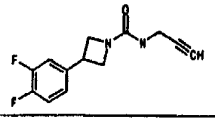
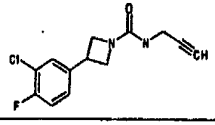
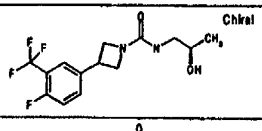
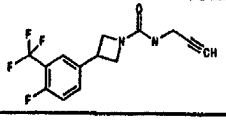
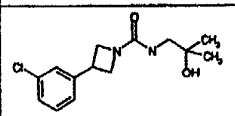
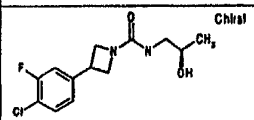
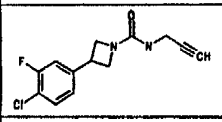
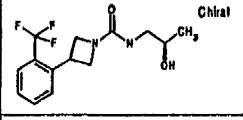
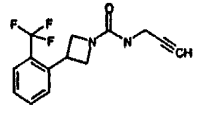
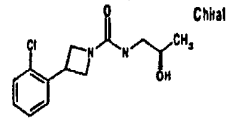
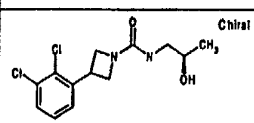
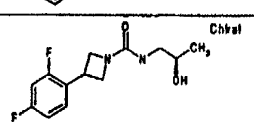
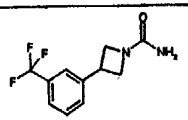
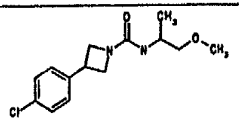
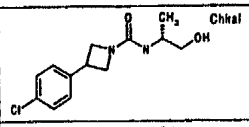
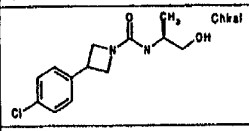
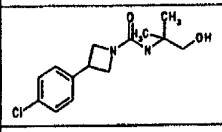
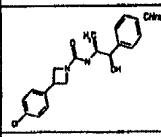
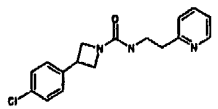
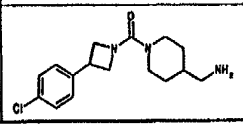
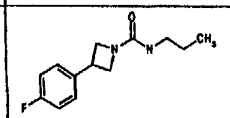
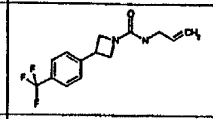
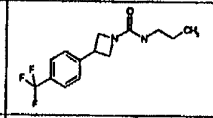
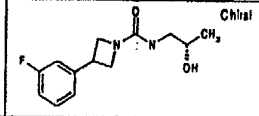
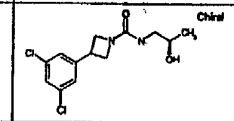
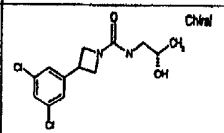
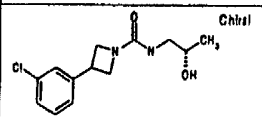
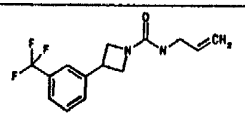
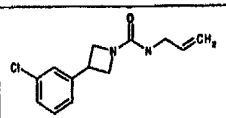
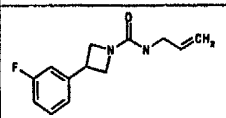
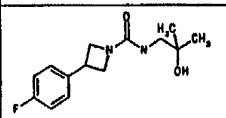
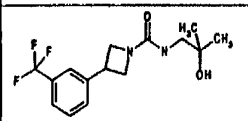
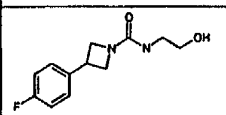
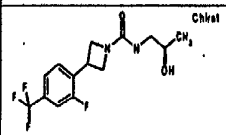
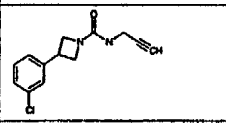
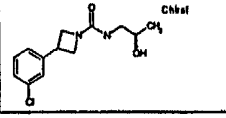
Table 1

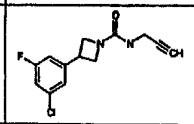
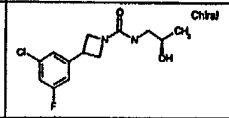
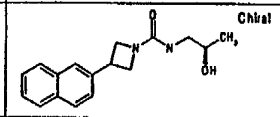
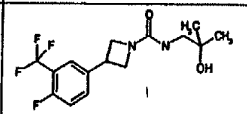
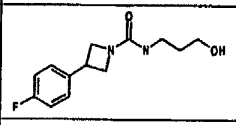
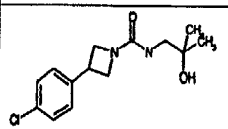
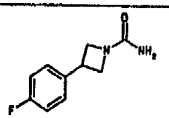
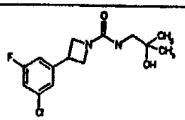
Example No.	Compound No.	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	Note
21	43		C13H16F2N2O2	270.28	108-109	57.79	5.96	10.28	57.77	5.97	10.36	
22	44		C13H16F2N2O2	270.28	108-109	57.73	5.95	10.29	57.77	5.97	10.36	
23	45		C13H16ClFN2O2	286.74	83-84	54.44	5.65	9.74	54.46	5.62	9.77	
24	46		C13H16ClFN2O2	286.74	83-84	54.46	5.69	9.63	54.46	5.62	9.77	
25	47		C13H12F2N2O	250.25	123.0	62.36	4.81	11.20	62.40	4.83	11.19	
26	48		C13H12ClFN2O	266.70	133.0	58.56	4.53	10.45	58.55	4.53	10.50	
27	49		C14H16F4N2O2	320.29	69-71	52.44	5.02	8.69	52.50	5.03	8.74	
28	50		C14H12F4N2O	300.26	119.0	56.05	4.02	9.26	56.00	4.03	9.33	

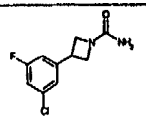
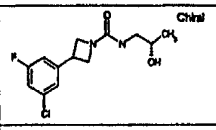
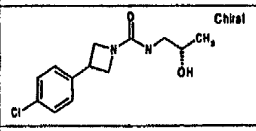
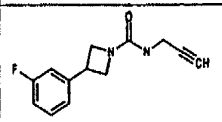
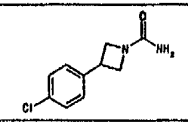
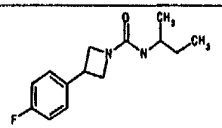
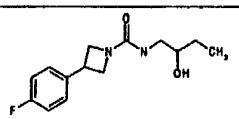
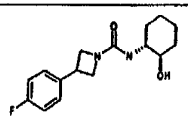
Example No.	Compound No.	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	Note
29	51		C14H19ClN2O2	282.77	102.0	59.69	6.69	9.80	59.47	6.77	9.90	
30	52		C13H16ClFN2O2	286.74	oil							a
31	53		C13H12ClFN2O	266.70	132.0	58.53	4.58	10.45	58.55	4.53	10.50	
32	54		C14H17F3N2O2	302.30	89.0	55.65	5.64	9.20	55.63	5.67	9.26	
33	55		C14H13F3N2O	282.27	101.0	59.70	4.55	9.96	59.57	4.64	9.92	
34	56		C13H17ClN2O2	268.75	109.0	57.15	6.35	10.28	58.10	6.38	10.42	
35	57		C13H16Cl2N2O2	303.19	111.0	51.43	5.24	9.19	51.50	5.32	9.24	
36	58		C13H16F2N2O2	270.28	88-89	57.74	6.11	10.34	57.77	5.97	10.36	

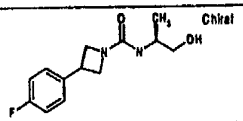
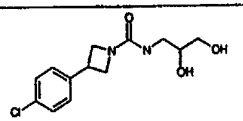
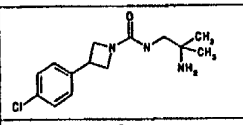
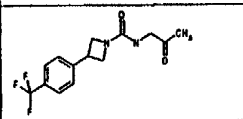
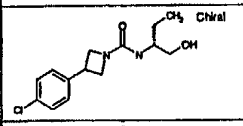
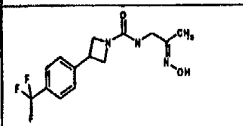
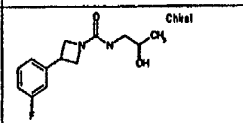
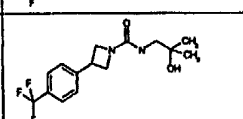
Example No.	Compound No.	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	Note
37	59		C11H11F3N2O	244.22	198.0	54.14	4.55	11.47	54.10	4.54	11.47	
38	60		C14H19ClN2O2	282.77	110.0	59.33	6.79	9.95	59.47	6.77	9.90	
39	61		C13H17ClN2O2	268.75	71-75							b
40	62		C13H17ClN2O2	268.75	82-85	58.09	6.41	10.36	58.10	6.38	10.42	
41	63		C14H19ClN2O2	282.77	134-135	59.31	6.86	10.02	59.47	6.77	9.90	
42	64		C19H21ClN2O2	344.84	120-122							c
43	65		C17H18ClN3O	315.81	125.0	64.75	5.74	13.27	64.66	5.74	13.30	
44	66		C16H22ClN3O	307.83	137-138	49.82	6.33	10.13	50.55	6.49	10.40	

Example No.	Compound No.	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	Note
45	67		C13H17FN2O	236.29	117-118.5	66.12	7.18	11.83	66.08	7.25	11.86	
46	68		C14H15F3N2O	284.28	136-137.5	59.26	5.39	9.93	59.15	5.32	9.85	
47	69		C14H17F3N2O	286.30	127-128.5	58.69	5.89	10.03	58.73	5.98	9.78	
48	70		C13H17FN2O2	252.29	79.5-80	61.91	6.77	11.09	61.89	6.79	11.10	
49	71		C13H16Cl2N2O2	303.19	110-111	51.67	5.35	9.21	51.50	5.32	9.24	
50	72		C13H16Cl2N2O2	303.19	110-111	52.00	5.41	9.24	51.50	5.32	9.24	
51	73		C13H17ClN2O2	268.75	78-80	58.44	6.13	10.39	58.10	6.38	10.42	
52	74		C14H15F3N2O	284.28	64-66	58.94	5.32	10.15	59.15	5.32	9.85	

Example No.	Compound No.	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	Note
53	75		C13H15ClN2O	250.73	65-66	62.75	5.97	11.09	62.28	6.03	11.17	
54	76		C13H15FN2O	234.28	62.5-63.5	66.52	6.52	11.90	66.65	6.45	11.95	
55	77		C14H19FN2O2	266.32	77-78.5	63.25	7.25	10.52	63.14	7.19	10.51	
56	78		C15H19F3N2O2	316.33	94.5-96	57.00	5.85	8.82	56.96	6.05	8.85	
57	79		C12H15FN2O2	238.26	99-101	60.41	6.35	11.72	60.49	6.35	11.75	
58	80		C14H16F4N2O2	320.29	106-107	52.41	5.11	8.71	52.50	5.03	8.74	
59	81		C13H13ClN2O	248.71	90-105 decom.	62.67	5.27	11.10	62.78	5.27	11.26	
60	82		C13H17ClN2O2	268.75	75-76.5	58.18	6.38	10.32	58.10	6.38	10.42	

Example No.	Compound No.	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	Note
61	83		C13H12ClFN2O	266.70	108.5-110	58.50	4.44	10.53	58.55	4.53	10.50	
62	84		C13H16ClFN2O2	286.74	79-80.5	54.61	5.77	9.69	54.46	5.62	9.77	
63	85		C17H20N2O2	284.36	143-144	71.63	7.11	9.78	71.81	7.09	9.85	
64	86		C15H18F4N2O2	334.32	110-111.5	53.85	5.51	8.34	53.89	5.42	8.38	
65	87		C13H17FN2O2	252.29	90-93	62.09	6.70	10.78	61.89	6.79	11.10	
66	88		C14H19ClN2O2	282.77	114-115.5	59.52	6.88	9.62	59.47	6.77	9.91	
67	89		C10H11FN2O	194.21	205-208.5	61.74	5.70	14.21	61.85	5.71	14.42	
68	90		C14H18ClFN2O2	300.76	112.5-113.5	55.86	6.07	9.33	55.91	6.03	9.31	

Example No.	Compound No.	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	Note
69	91		C10H10ClFN2O	228.66	198-200.5							
70	92		C13H16ClFN2O2	286.74	81-82.5							
71	93		C13H17ClN2O2	268.75	92.5-94	58.23	6.41	10.26	58.10	6.38	10.42	
72	94		C13H13FN2O	232.26	101.5-10.25	67.13	5.60	12.03	67.23	5.64	12.06	
73	95		C10H11ClN2O	210.66	oil							d
74	96		C14H19FN2O	250.32	100-102	67.10	7.64	11.05	67.18	7.65	11.19	
75	97		C14H19FN2O2 (0.3 H2O)	266.32	77-79	61.83	7.30	10.39	61.74	7.28	10.29	
76	98		C16H21FN2O2	292.36	141-142.5	65.71	7.31	9.52	65.73	7.24	9.58	

Example No.	Compound No.	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	Note
77	99		C13H17FN2O2	252.29	118-120	61.59	6.89	10.95	61.89	6.79	11.10	
78	100		C13H17ClN2O3	284.75	90-92	54.93	6.07	9.79	54.84	6.02	9.83	
79	101		C14H20ClN3O.HCl	318.25	183-184	52.76	6.77	13.04	52.84	6.65	13.20	
80	102		C14H15F3N2O2	300.28	139.5-141	56.07	5.05	9.27	56.00	5.03	9.32	f
81	103		C14H19ClN2O2	282.77	oil							e
82	104		C14H16F3N3O2	315.30	>150 decom.	53.05	5.18	13.24	53.33	5.11	13.32	g
83	105		C13H17FN2O2	252.29	77.5-79	61.82	6.83	11.05	61.89	6.79	11.10	
84	106		C15H19F3N2O2	316.33	123-124	57.03	6.08	8.88	56.96	6.05	8.85	

Footnotes for Table 1:

Footnote a: IR: 3373, 3316, 2923, 2855, 1639, 1620, 1557, 1488, 1462, 1434, 1378, 1304, 1153, 815 cm^{-1}.

Footnote b: IR: 3500, 3429, 3346, 3274, 2925, 2854, 1614, 1556, 1466, 1420, 1407, 1052, 824, 536 cm^{-1}.

Footnote c: IR: 3414, 3320, 3253, 2925, 2855, 1606, 1544, 1492, 1460, 1376, 1316, 1092, 822, 751, 705 cm^{-1}.

Footnote d: IR: 3340, 3166, 2923, 2854, 1650, 1613, 1493, 1460, 1378, 1303, 1098, 820 cm^{-1}.

Footnote e: IR: 3310, 2964, 2878, 1632, 1538, 1494, 1482, 1462, 1398, 1328, 1093, 1015, 823, 529 cm^{-1}.

Footnote f: compound (102) was made by the oxidation of compound (33), by methods known to those skilled in the art.

Footnote g: compound (104) was made from compound (102) by methods known to those skilled in the art.

Testing Procedures

Rat transient middle cerebral artery occlusion (MCAo) ischaemia model

This model of middle cerebral artery occlusion used relies on an intraluminal filament technique in the rat (Zhao Q. *et al.*, *Acta Physiol. Scand.* **1994**, *152,* 349-350). Male Lister Hooded rats were used in these experiments and were divided into three groups (Group 1: vehicle; Group 2: chlomethiazole (CMZ); Group 3: a compound of formula I). The sample size in each was 11 to 15. The animal was anaesthetised and the carotid artery exposed. A heat rounded dermalon suture (3/0) of a specified diameter was introduced into the ligated carotid artery, past the bifurcations of the external and common carotid, the internal carotid and the pterygopalatine artery, into the intracranial circulation. The filament then lodged in the narrow proximal anterior carotid occluding the middle cerebral artery. After 90 min. of middle cerebral artery occlusion, the filament was removed, allowing re-circulation.

22.5 h following reperfusion, the animal was perfused *via* the transaortic route, using 200 ml of a 4 percent solution of tetrazolium chloride warmed to 37° C. Following perfusion, the brain was removed and immersion fixed in 10 percent formalin/saline for at least 48 h. Following fixation, the brain was sliced into 0.5 mm sections on a vibroslice. Using this technique, viable tissue was stained dark red and infarcted tissue remains unstained. The area of infarction on each section was measured, and the total volume of infarction in the hemisphere, cortex and striatum computed, using the Kontron image analysis system.

The experimental data are displayed in Figure 1 which shows the effect of (i) vehicle; (ii) 128 mg/kg of clomethiazole dosed intraperitoneally (i.p.); and (iii) 30 mg/kg i.p. of compound (Ib), on infarct volumes (assessed using tetrazolium histochemistry) after transient middle cerebral artery occlusion. Data are displayed as (mean + SEM) using absolute infarct volumes in mm^3. In Figure 1, ** signifies $p < 0.01$, and * signifies $p < 0.05$ in the t test.

Figure 1 illustrates that compound (Ib) exhibits significant neuroprotection at a dose of 30 mg/kg i.p. in the rat transient MCAo model. Clomethiazole at a dose of 128 mg/kg i.p. was found not to be effective in this model (see Sydserff, S.G. *et al.,. Br. J. Pharmacol.* **1995**, *114*, 1631-1635).

Mouse permanent middle cerebral artery occlusion ischaemia model

Adult male C57Bl mice (20-25 g, n = 10 per group) were administered a compound of formula (I) (10 mg/kg) or vehicle (60% PEG400 in water) i.p. 30 minutes prior to middle cerebral artery (MCA) occlusion. Under halothane anaesthesia (1.5% halothane in nitrous oxide: oxygen (70:30)), a small craniectomy was made to expose the left MCA. The distal portion of the MCA was occluded by electrocoagulation. The incision site was sutured and anaesthetics withdrawn. 24 h following MCA occlusion, the mouse was euthanised, the brain removed and immersed in 4% tetrazolium chloride to visualise the area of infarction (Backhaus C. *et al.*, *J. Pharm Methods* **1992**, *27*, 27-32). Brains were then stored in 10% formalin/saline. The area of infarction as visible on the cortical surface was then computed using a PC digital imaging system (KS300, Imaging Associates, UK). Data generated is absolute area of infraction in mm^2 for each animal. Mean infarct areas were compared by unpaired t-tests with significance taken at $p < 0.05$.

The experimental results are displayed in Figure 2 which shows the effect of (i) vehicle; and (ii) 60 mg/kg i.p. of compound (Ib) on infarction after permanent middle cerebral artery occlusion.

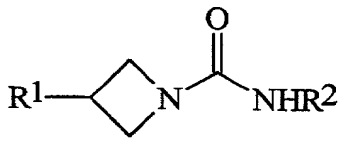
Figure 2 shows that that compound (Ib) exhibits significant neuroprotection at a dose of 60 mg/kg i.p. in the mouse permanent MCAo model.

Further experiments have shown that the following compounds produce significant neuroprotection at a dose of <100mg/kg in the mouse permanent middle cerebral artery occlusion ischaemia model:

(R)-3-(4-Fluorophenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide (20);
(3-(4-Chlorophenyl)-*N*-(2-propynyl)azetidine-1-carboxamide (21);
(*S*)-3-(4-Fluorophenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide (23); and
(S)-3-(4-(Trifluoromethyl)phenyl)-*N*-(2-hydroxypropyl)azetidine carboxamide (34).

CLAIMS

1. Use of a compound of formula (I)



(I)

wherein

R^1 is aryl; and

R^2 is hydrogen or alkyl;

or a pharmaceutically acceptable salt or prodrug thereof in the manufacture of a medicament for neuroprotection in a subject or for the treatment of cerebral ischaemia, central nervous system injury or eye diseases.

2. A use according to claim 1 wherein R^1 is an aryl group selected from phenyl and naphthyl.

3. A use acording to claim 1 or 2 wherein R^1 has 1, 2 or 3 substituent groups.

4. A use according to any preceding claim wherein R^1 is substituted with one or more substituent groups selected from halo, trifluoromethyl and tertiary-butyl.

5. A use according to claim 4 wherein said halo groups are selected from chloro and fluoro.

6. A use according to claim 1, 2, 3, 4 or 5 wherein R^1 is a meta- or para-substituted phenyl group.

7. A use according to claim 1 wherein R^1 is selected from 4-chlorophenyl, 4-fluorophenyl, 4-(trifluoromethyl)phenyl and 3-(trifluoromethyl)phenyl.

8. A use according to claim 1, 2, 3, 4 or 5 wherein R^1 is selected from a 2,3-disubstituted phenyl group, a 2,4-disubstituted phenyl group, a 3,4-disubstituted phenyl group and a 3,5-disubstituted phenyl group.

9. A use according to claim 8 wherein R^1 is substituted by two halo groups, the same or different, or by one halo group and one trifluoromethyl group.

10. A use according to claim 9 wherein R^1 is dichloro-substituted, difluoro-substituted, chloro-fluoro-substituted or fluoro-trifluoromethyl-substituted.

11. A use according to claim 1 wherein R^1 is selected from 3,4-dichlorophenyl, 3,4-difluorophenyl, 3-chloro-4-fluorophenyl, 4-chloro-3-fluorophenyl, 3-fluoro-4-(trifluoromethyl)phenyl, 4-fluoro-3-(trifluoromethyl)phenyl and 3-chloro-5-fluorophenyl.

12. A use according to any one of claims 1 to 11 wherein R^2 is alkyl.

13. A use according to any one of claims 1 to 12 wherein R^2 is C_{1-8} alkyl.

14. A use according to any one of claims 1 to 13 wherein R^2 is alkenyl, alkynyl, hydroxyalkyl or alkoxyalkyl.

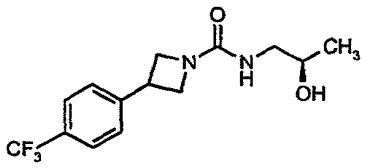
15. A use according to any one of claims 1 to 13 wherein R^2 is unsubstituted saturated cyclic or acyclic hydrocarbyl.

16. A use according to any one of claims 1 to 13 wherein R^2 is propyl, 2-propenyl, 2-propynyl or 2-hydroxypropyl.

17. A use according to claim 1 wherein the compound of formula (I) is selected from:
(R)-3-(4-Fluorophenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide;
(3-(4-Chlorophenyl)-*N*-(2-propynyl)azetidine-1-carboxamide;
(*S*)-3-(4-Fluorophenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide; and
(S)-3-(4-(Trifluoromethyl)phenyl)-*N*-(2-hydroxypropyl)azetidine carboxamide, or a pharmaceutically acceptable salt or prodrug thereof.

18. A use according to claim 1 wherein the compound of formula (I) is 3-(4-(trifluoromethyl)phenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide or a pharmaceutically acceptable salt or prodrug thereof.

19. A use according to claim 1 wherein the compound of formula (I) is the (*R*) enantiomer of 3-(4-(trifluoromethyl)phenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide **(Ib)**



(Ib)

or a pharmaceutically acceptable salt or prodrug thereof, substantially free of its (*S*)-enantiomer.

20. A use according to any preceding claim wherein said medicament comprises a pharmaceutically acceptable carrier and as active ingredient an effective amount of compound (I).

21. A use according to claim 20 wherein said carrier comprises a cyclodextrin or an ether derivative thereof.

22. A use according to any preceding claim wherein the medicament further comprises a buffer system, an isotonizing agent and water.

23. Use according to any of preceding claim wherein the compound of formula (I) is in combination with one or more additional drugs useful in neuroprotection or in the treatment of cerebral ischaemia, central nervous system injury or eye diseases, the components being in the same formulation or in separate formulations for administration simultaneously or sequentially.

24. A method of neuroprotection comprising administration to a subject in need of such treatment an effective dose of a compound of formula (I) as set out in any of claims 1 to 19, or a pharmaceutically acceptable salt or prodrug thereof.

25. A method of treatment of cerebral ischaemia, central nervous system injury or eye diseases comprising administration to a subject in need of such treatment an effective dose of a compound of formula (I) as set out in any of claims 1 to 19, or a pharmaceutically acceptable salt or prodrug thereof.

26. A method according to claim 24 or 25 wherein the compound of formula (I) is administered in the form as set out in any of claims 20, 21 or 22.

United States Patent [19]

Taylor, Jr. et al.

[11] **Patent Number: 4,956,359**

[45] **Date of Patent: Sep. 11, 1990**

[54] **3-ARYLOXY AND 3-ARYLTHIOAZETIDINECARBOXAMIDES AS ANTICONVULSANTS AND ANTIEPILEPTICS**

[75] Inventors: **Chandler R. Taylor, Jr.; Albert D. Cale, Jr.**, both of Mechanicsville; **Harold F. Stauffer, Jr.**, Midlothian, all of Va.

[73] Assignee: **A. H. Robins Company, Inc.**, Richmond, Va.

[21] Appl. No.: **921,466**

[22] Filed: **Oct. 22, 1986**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 706,621, Feb. 28, 1985, abandoned.

[51] **Int. Cl.**[5] **A61K 31/395**

[52] **U.S. Cl.** **514/210;** 540/515; 540/596; 544/111; 544/349; 544/359; 546/208; 546/256; 546/275; 548/336; 548/524; 548/952

[58] **Field of Search** 514/210; 540/575, 596; 544/111, 349, 359; 546/208, 256, 275; 548/336, 524, 952

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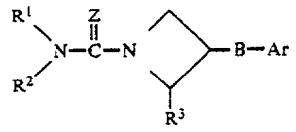
Primary Examiner—Mukund J. Shah
Assistant Examiner—C. L. Cseh

[57] **ABSTRACT**

Novel 3-aryloxy and 3-arylthioazetidinecarboxamides having utility in a method of treating convulsions and epilepsy and compositions therefor are disclosed having the formula:



wherein Z is oxygen or sulfur; B is oxygen or sulfur; Ar is pyridyl or halo-substituted-pyridyl, phenyl or substituted phenyl; R^1 and R^2 are selected from hydrogen, loweralkyl, aryl, allyl, substituted allyl, propargyl, cycloalkyl, loweralkylcycloalkyl, cycloalkylloweralkyl, arylloweralkyl, diloweralkylaminoloweralkyl, and R^1 and R^2 when taken with the adjacent nitrogen atom may form a heterocyclic radical; R^3 is hydrogen, loweralkyl, aryl or arylloweralkyl, and the geometrical isomers thereof, excepting that when R^3 is hydrogen, Z is oxygen, B is oxygen, and Ar is phenyl or phenyl substituted by trifluoromethyl or aminocarbonyl, then R^1 and R^2 cannot be a combination of hydrogen and loweralkyl, and the further exception that when R^3 is hydrogen, Z is oxygen, B is oxygen, and Ar is phenyl or phenyl substituted by fluoro, loweralkyl, loweralkoxy, trifluoromethyl, acetyl, or aminocarbonyl, then R^1 and R^2 cannot both be hydrogen.

94 Claims, No Drawings

Figure 1

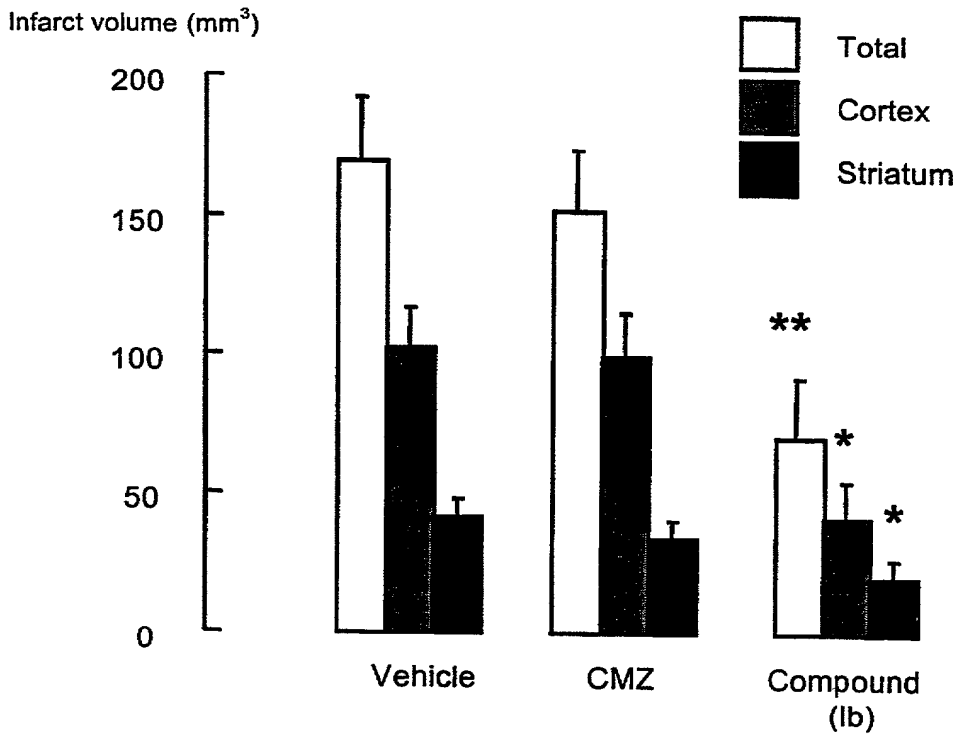
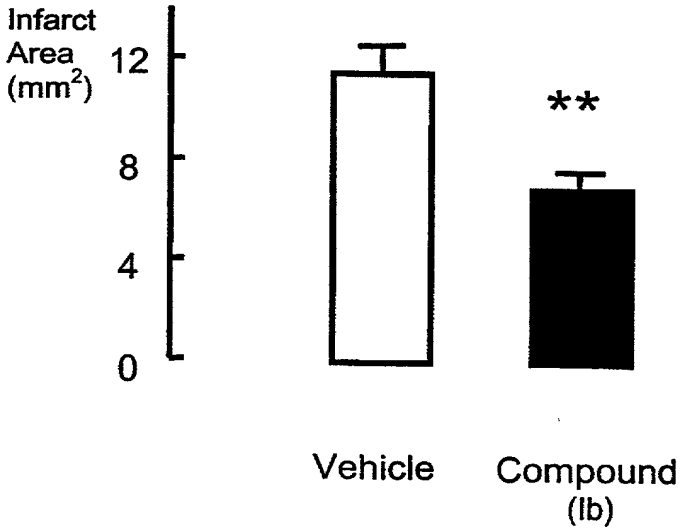


Figure 2



DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I HEREBY DECLARE:

THAT my residence, post office address, and citizenship are as stated below next to my name;

THAT I believe I am the original, first, and sole inventor (if only one inventor is named below) or an original, first, and joint inventor (if plural inventors are named below or in an attached Declaration) of the subject matter which is claimed and for which a patent is sought on the invention entitled

CHEMICAL COMPOUNDS-III

(Attorney Docket No. 040283-0199)

the specification of which (check one)

___ Is attached hereto.

__X__ Was filed on July 21, 2000 as United States Application Number or PCT International Application Number PCT/GB00/02817 and was amended on _____ (if applicable).

THAT I do not know and do not believe that the same invention was ever known or used by others in the United States of America, or was patented or described in any printed publication in any country, before I (we) invented it;

THAT I do not know and do not believe that the same invention was patented or described in any printed publication in any country, or in public use or on sale in the United States of America, for more than one year prior to the filing date of this United States application;

THAT I do not know and do not believe that the same invention was first patented or made the subject of an inventor's certificate that issued in any country foreign to the United States of America before the filing date of this United States application if the foreign application was filed by me (us), or by my (our) legal representatives or assigns, more than twelve months (six months for design patents) prior to the filing date of this United States application;

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THAT I acknowledge the duty to disclose to the U.S. Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I HEREBY CLAIM foreign priority benefits under Title 35, United States Code §119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below any foreign application for patent or inventor's certificate or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number	Country	Foreign Filing Date	Priority Claimed?	Certified Copy Attached?
9917384.1	Great Britain	07/23/1999	YES	

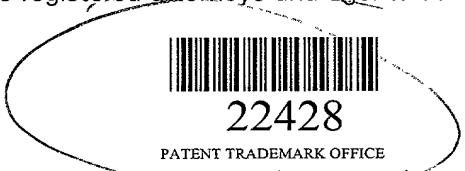
I HEREBY CLAIM the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below.

U.S. Provisional Application Number	Filing Date

I HEREBY CLAIM the benefit under Title 35, United States Code, §120 of any United States application(s), or § 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application Number	PCT Parent Application Number	Parent Filing Date	Parent Patent Number

I HEREBY APPOINT the registered attorneys and agents at Customer Number 22428



to have full power to prosecute this application and any continuations, divisions, reissues, and reexaminations thereof, to receive the patent, and to transact all business in the United States Patent and Trademark Office connected therewith.

I request that all correspondence be directed to:

Bernhard D. Saxe
FOLEY & LARDNER
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22428

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I UNDERSTAND AND AGREE THAT the foregoing attorneys and agents appointed by me to prosecute this application do not personally represent me or my legal interests, but instead represent the interests of the legal owner(s) of the invention described in this application.

I FURTHER DECLARE THAT all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

1-00

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Date	18th April 2002